Reagents for Organic Synthesis

VOLUME 5

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PREFACE

This volume covers literature for the most part from 1972 to August 1974. It includes references to about 350 reagents discussed by us for the first time as well as new references to about 400 reagents previously discussed. During this period interesting reagents based on selenium have been introduced. A useful organotin reagent has been introduced for synthesis of acetylenes. Phase-transfer catalysts and crown ethers have continued to be extremely useful in organic chemistry.

We are indebted to colleagues who have furnished additional information or suggested topics for inclusion. We are particularly grateful to James L. Heck and Dr. Susan Brachwitz, who read large parts of the manuscript and offered many helpful suggestions. Professor John A. Secrist, Dr. William Moberg, Dr. Mark A. Wuonola, Robert H. Wollenberg, and Rick L. Danheiser, all of whom read proof of Volume 4, have performed the same service for this volume. In addition Thomas Hoye, Oljan Repič, Dr. James B. Doherty, Dr. William J. Greenlee, and William Stiggs have read the proof. All these chemists have been extremely helpful.

Lenor Kirkeby and Laura Gordon typed the manuscript and drew the formulas.

CONTENTS

Introduction

Most of the suppliers listed in the text can be found in the section on suppliers in Vol. **3**, 345–348. A few additional suppliers are included in **4**, 580.

The latest abbreviations for journals used in *Reagents* are listed in **4**, 2.

On the whole, we have tried to avoid abbreviations for chemical names. However, use of DMF, THF, NBS, HMPT, and some other symbols has probably resulted in some saving of space. The most frequently used abbreviations are shown in the accompanying list.

Abbreviations

|	
Ac	CH_3CO- (acetyl)
BOC	.t-Butyloxycarbonyl
Bz	C_6H_5CO- (benzoyl)
CAN	Ceric ammonium nitrate
Cathyl	Carboethoxy
CBZ	Carbobenzyloxy
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0]nonene-5
DBU	1,5-Diazabicyclo[5.4.0]undecene-5
DCC	Dicyclohexylcarbodiimide
DDQ	.2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Diglyme	Diethylene glycol dimethyl ether
DMA	Dimethylacetamide
DME	Dimethoxyethane (glyme)
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNP	2,4-Dinitrophenylhydrazine
HMPT	Hexamethylphosphoric triamide
LDA	Lithium diisopropylamide
MMC	Magnesium methyl carbonate
Ms	CH_3SO_2- (mesyl)
NBA	N-Bromoacetamide
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
Phth	Phthaloyl
PPA	Polyphosphoric acid
PPE	Polyphosphate ester
Py	Pyridine
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane

TMEDA   N,N,N',N'-Tetramethylethylenediamine
Triglyme   Triethylene glycol dimethyl ether
Trityl $(C_6H_5)_3C-$
Ts p-$CH_3C_6H_4SO_2-$ (tosyl)
TTFA   Thallium(III) trifluoroacetate

A

Acetic acid, 2, 5–7.

Purine synthesis.[1] 5-Amino-4-acylaminopyrimidines (1) are cyclized to purines (2) in high yield by acetic acid in refluxing ethanol.

(1)   (2)
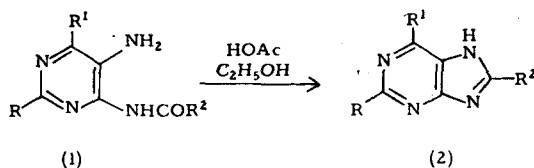
[1]F. L. Kempter, H. Rokos, and W. Pfleiderer, *Ber.*, **103**, 885 (1970).

Acetic anhydride, 1, 3; 2, 7–10.

β-Carbonyl enamines.[1] β-Carbonyl enamines can be obtained by application of the Polonovski reaction (2, 7). Thus the reaction of N-methylpiperidone-4 (1) with *m*-chloroperbenzoic acid in CH_2Cl_2 at −40° and then with acetic anhydride

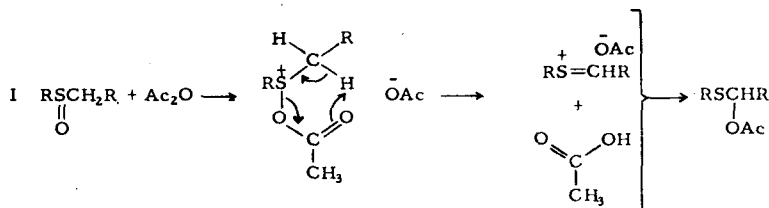(1)   (2)
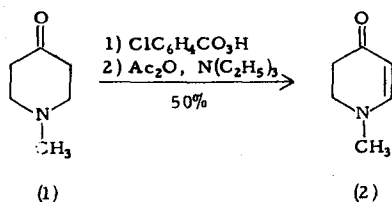
and triethylamine at −40° and then at 0° gives the pyridinone (2) in about 50% yield.

This approach was first discovered in the case of derivatives of lysergic acid.
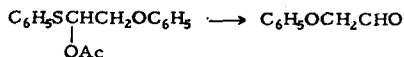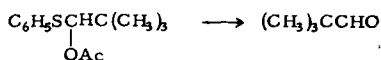
Pummerer reaction. The reaction of a sulfoxide bearing at least one α-hydrogen with hot acetic anhydride leads to an α-acetoxy sulfide.

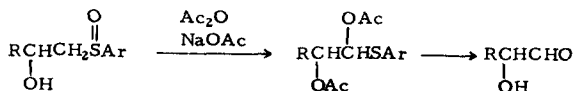Parham and Edwards[2] have suggested the mechanism shown in scheme I.

The products of the rearrangement are convertible into aldehydes by acidic or basic hydrolysis, but this reaction has been used mainly to establish structures.

$$C_6H_5SCHC(CH_3)_3 \longrightarrow (CH_3)_3CCHO$$
$$\overset{|}{O}Ac$$

$$C_6H_5SCHCH_2OC_6H_5 \longrightarrow C_6H_5OCH_2CHO$$
$$\overset{|}{O}Ac$$

Japanese chemists[3] have reported that β-hydroxy sulfoxides undergo the Pummerer reaction if sodium acetate is added to give α,β-diacetoxy sulfides, which are protected forms of α-hydroxy aldehydes.

$$\underset{\overset{|}{OH}}{RCHCH_2\overset{\overset{O}{||}}{S}Ar} \xrightarrow[NaOAc]{Ac_2O} \underset{\overset{|}{OAc}}{RCH\overset{\overset{OAc}{|}}{C}HSAr} \longrightarrow \underset{\overset{|}{OH}}{RCHCHO}$$
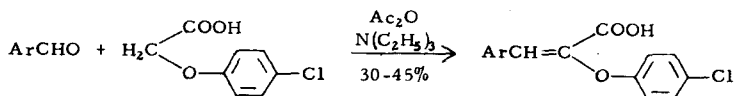
[1] P. Stütz and P. A. Stadler, *Tetrahedron Letters*, 5095 (1973).
[2] W. E. Parham and L. D. Edwards, *J. Org.*, **33**, 4150 (1968).
[3] S. Iruichijima, K. Maniwa, and G. Tsuchihashi, *Am. Soc.*, **96**, 4280 (1974).

Acetic anhydride–Triethylamine.

Modified Perkin reaction.[1] α-(4'-Chlorophenoxy)cinnamic acids (1) can be obtained in a rather low yield by condensation of benzaldehydes and 4'-chlorophenoxyacetic acid in a boiling mixture of acetic anhydride and triethylamine.[2]

$$ArCHO + H_2C\overset{COOH}{\underset{O-\bigcirc-Cl}{}} \xrightarrow[30-45\%]{\overset{Ac_2O}{N(C_2H_5)_3}} ArCH=C\overset{COOH}{\underset{O-\bigcirc-Cl}{}}$$

(1)

[1] L. F. Fieser and M. Fieser, *Advanced Organic Chemistry*, Reinhold, New York, 464–466 (1961).
[2] M. Flammang, C.-G. Wermuth, and J. Schreiber, *Bull. soc.*, 4619 (1972).

Acetyl chloride, 1, 11; 4, 5–6.

Sulfides from sulfoxides and sulfilimines.[1]   Sulfoxides and sulfilimines are reduced to sulfides in high yields by excess acetyl chloride in methylene chloride at 20°.

$$\underset{C_6H_5}{\overset{C_6H_5}{}}S=O + 2\,CH_3COCl \xrightarrow[\sim100\%]{\overset{CH_2Cl_2}{20^0}} \underset{C_6H_5}{\overset{C_6H_5}{}}S + Cl_2 + \underset{CH_3C\overset{O}{\diagdown}}{\overset{CH_3C\diagup^O}{}}O$$

$$C_6H_5 \diagdown S=NTs \xrightarrow[\sim 100\%]{2 \ CH_3COCl} \ C_6H_5 \diagdown S + Cl_2 + \ CH_3C \diagup NTs$$

'T. Numata and S. Oae, *Chem. Ind.*, 277 (1973).

Acetyl methanesulfonate, $CH_3COOSO_2CH_3$. Mol. wt. 138.14, b.p. 100°/0.05 mm. Supplier: WBL.

The reagent is prepared in 85% yield by the reaction of methanesulfonic acid and acetyl chloride (reflux 16 hr.).[1]

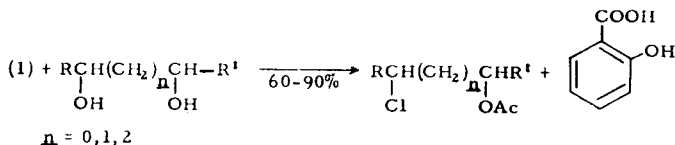*Ether cleavage.* This substance, like acetyl *p*-toluenesulfonate (2, 14–15; 4, 8), readily cleaves aliphatic ethers[2]:

$$C_2H_5O(CH_2)_3CH_3 \xrightarrow[130°]{CH_3COOSO_2CH_3} CH_3COOC_2H_5 + CH_3COO(CH_2)_3CH_3$$
$$47\% \qquad\qquad 19\%$$

Reaction with aromatic ethers. The reagent reacts with aromatic ethers under mild conditions to give monoacylated derivatives, which undergo self-condensation to triphenylbenzenes under vigorous conditions.[3]

(±)-*Cedrone.*[4] Treatment of (1) with acetyl methanesulfonate followed by aqueous workup gives (±)-cedrone (2) and (±)-epicedrone (3) in 85% yield. The cyclization can also be effected with the diastereomeric forms of (1) and in each case the cyclization proved to be stereospecific. Use of formic acid, BF_3, or $SnCl_4$ gave very low yields of cedrone.[5,6]

(1)   (2)   (3)

[1] M. H. Karger and Y. Mazur, *J. Org.*, **36**, 528 (1971).
[2] *Idem, ibid.*, **36**, 532 (1971).
[3] *Idem, ibid.*, **36**, 540 (1971).
[4] E. J. Corey and R. D. Balanson, *Tetrahedron Letters*, 3153 (1973).
[5] E. J. Corey, N. N. Girotra, and C. T. Mathew, *Am. Soc.*, **91**, 1557 (1969).
[6] G. Stork and P. Grieco, *ibid.*, **91**, 2407 (1969); G. Stork and M. Marx, *ibid.*, **91**, 2371 (1969); G. Stork and M. Gregson, *ibid.*, **91**, 2373 (1969).

2-Acetylsalicylic acid chloride,

$$\text{COCl} \quad \text{OAc}$$

(1)
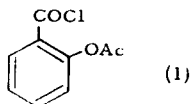
Mol. wt. 198.61, m.p. 46–49°. Suppliers: Aldrich, Fluka.

The reagent reacts with 1,2-, 1,3-, and 1,4-diols to give β-, γ-, and δ-chloroalkyl

$$(1) + \text{RCH(CH}_2)_n\text{CH}-\text{R}^1 \xrightarrow[60-90\%]{} \text{RCH(CH}_2)_n\text{CHR}^1 + \begin{array}{c}\text{COOH}\\\text{OH}\end{array}$$

$$\underset{\text{OH}}{}\quad\underset{\text{OH}}{} \qquad \underset{\text{Cl}}{}\quad\underset{\text{OAc}}{}$$

$\underline{n} = 0, 1, 2$

acetates and salicylic acid. Alcohols are converted into approximately equal amounts of the corresponding alkyl chlorides and acetates.[1]

[1] A. A. Akhrem, V. V. Zharkov, G. V. Zaitseva, and I. A. Mikhailopulo, *Tetrahedron Letters*, 1475 (1973).

β-**Alanine**, $H_2NCH_2CH_2COOH$. Mol. wt. 89.10, m.p. 198° dec. Suppliers: Aldrich, Baker, Columbia, Eastman, E. M. Labs., Fisher, K and K, MCB, ROC/RIC.

Knoevenagel reaction.[1] Condensation of (+)-3-methylcyclohexanone (1) with malononitrile in 95% ethanol proceeds slowly at room temperature to give (−)-3-methylcyclohexylidenemalononitrile (2) in 80–85% yield. The reaction is


$$(1,\ \alpha_D\ +9.37°) \qquad\qquad (2,\ \alpha_D\ -80.4°)$$
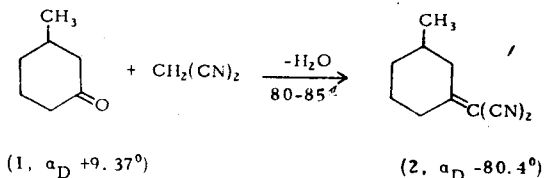
efficiently catalyzed by weak bases (β-alanine, NH_4OAc); strong bases (NaOAc, KOAc, KF, piperidine) effect more rapid condensation, but promote telomerization of malononitrile.[2]
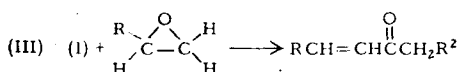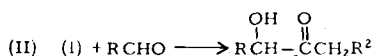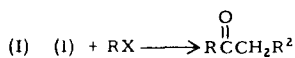
[1] G. Jones, *Org. React.*, 15, 204 (1967).
[2] F. S. Prout, V. D. Beaucaire, G. R. Dyrkacz, W. M. Koppes, R. E. Kuznicki, T. A. Marlewski, J. J. Pienkowski, and J. M. Puda, *J. Org.*, 38, 1512 (1973).

1-(**Alkylthio**)**vinyllithium**, $R^1SC = CHR^2$ (1).
$$\underset{\text{Li}}{}$$

The reagents are prepared by addition of *sec*-butyllithium to a solution of a vinyl sulfide in THF–HMPT (9:1) at −78°. They are stable at this temperature for at least 6 hr. Other solvent systems were less satisfactory.

$$(1) \quad R^1SCH=CHR^2 \xrightarrow[\text{THF-HMPT}]{\text{sec-BuLi}} R^1SC=CHR^2$$
$$\underset{Li}{|}$$
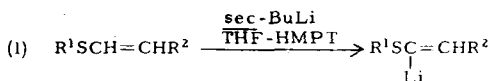
Synthesis of ketones.[1]   The reagent (1) reacts with alkyl halides, aldehydes, and epoxides to give, after hydrolysis with mercuric chloride in aqueous acetonit-

$$(I) \quad (1) + RX \longrightarrow R\overset{\overset{\displaystyle O}{\|}}{C}CH_2R^2$$

$$(II) \quad (1) + RCHO \longrightarrow R\overset{\overset{\displaystyle OH}{|}}{C}H-\overset{\overset{\displaystyle O}{\|}}{C}CH_2R^2$$

$$(III) \quad (1) + \underset{H}{\overset{R}{\diagdown}}C-\underset{H}{\overset{O}{\diagup}}\overset{H}{\diagup}C\overset{H}{\diagdown} \longrightarrow RCH=CH\overset{\overset{\displaystyle O}{\|}}{C}CH_2R^2$$

rile (3, 97), ketones (I), acyloins (II), and α,β-unsaturated ketones (III), respectively. Yields are in the range 50–90%.

[1] K. Oshima, K. Shimoji, H. Takahashi, H. Yamamoto, and H. Nozaki, *Am. Soc.*, **95**, 2694 (1973).

Allylidenetriphenylphosphorane, $CH_2=CHCH=P(C_6H_5)_3$ (1). Mol. wt. 302.34.

  Preparation. This Wittig reagent is prepared[1] preferably from allylidene-triphenylphosphonium chloride, $CH_2=CH-CH_2P(C_6H_5)_3Cl^-$,[2] by treatment with *n*-butyllithium.
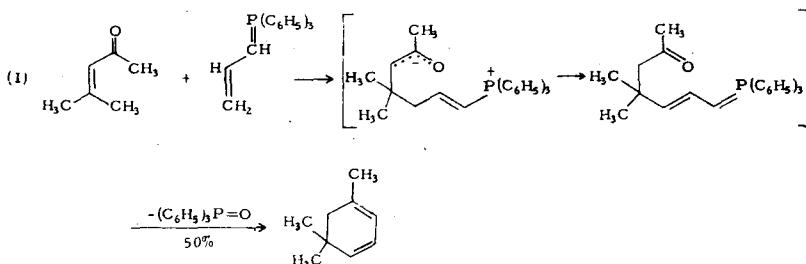
  1,3-Cyclohexadienes.[1] This ylide reacts with ethyl α-isopropylidene-acetoacetate (2) to give ethyl α-safranate (3) in 60% yield. The reaction involves
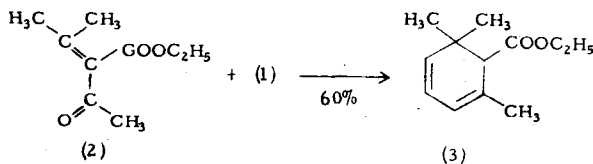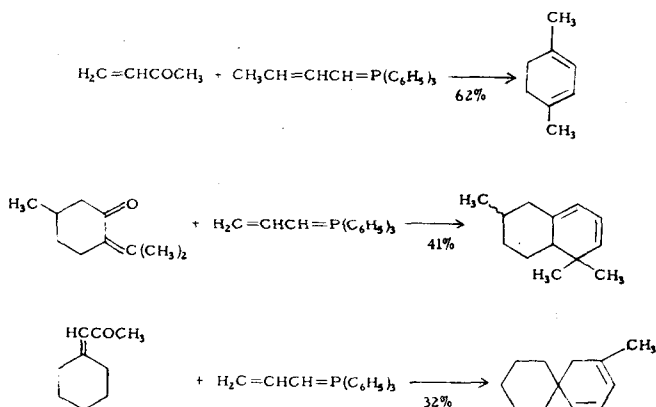

initial addition from the γ-position of the ylide, rather than the more hindered α-position, and the β-position of the conjugated ketone to give a phosphonium betaine (a).
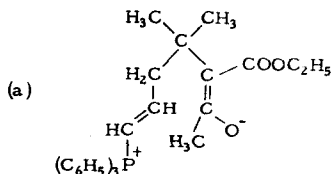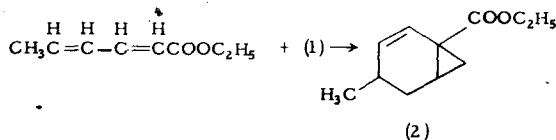
Dauben *et al.*[3] have shown this synthesis to be a general reaction as formulated in equation I.
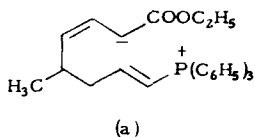

(I)

Other examples:

$H_2C=CHCOCH_3$ + $CH_3CH=CHCH=P(C_6H_5)_3$ $\xrightarrow{62\%}$

+ $H_2C=CHCH=P(C_6H_5)_3$ $\xrightarrow{41\%}$
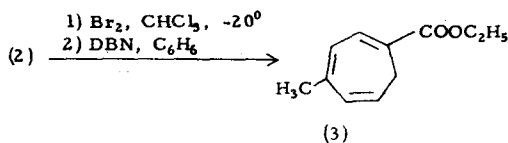

+ $H_2C=CHCH=P(C_6H_5)_3$ $\xrightarrow{32\%}$

Conjugate addition to dienoic esters.[4]   Reaction of (1) with ethyl sorbate in THF (25°) gives the Δ²-norcarene (2) in about 30% yield. The reaction presumably

$$\begin{array}{c} \text{H H H H} \\ CH_3C=C-C=CCOOC_2H_5 \end{array} + (1) \longrightarrow$$

(2)

involves the dipolar intermediate (a). Bromination of (2) followed by dehydro-

(a)

bromination (DBN) gives the cycloheptatriene (3).

$$(2) \xrightarrow[\text{2) DBN, } C_6H_6]{\text{1) Br}_2, \text{ CHCl}_3, -20^0}$$

(3)

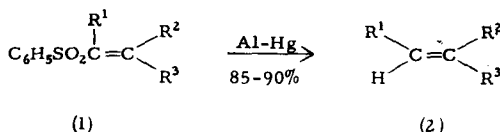[1]G. Büchi and H. Wüest, *Helv.*, **54**, 1767 (1971).
[2]This salt is obtained in 81% yield by refluxing triphenylphosphine in allyl chloride for 96 hr.
[3]W. G. Dauben, D. J. Hart, J. Ipaktschi, and A. P. Kozikowski, *Tetrahedron Letters*, 4425 (1973).
[4]W. G. Dauben and A. P. Kozikowski, *ibid.*, 3711 (1973).

Aluminum amalgam, 1, 20–21; 3, 7.

Olefin synthesis.[1] α,β-Unsaturated phenyl sulfones (1) in aqueous THF are reductively cleaved to olefins (2) in about 85% yield by treatment with aluminum

$$C_6H_5SO_2\underset{R^3}{\overset{R^1}{C}}=C\overset{R^2}{\underset{R^3}{\diagdown}} \xrightarrow[85-90\%]{\text{Al-Hg}} \underset{H}{\overset{R^1}{\diagdown}}C=C\overset{R^2}{\underset{R^3}{\diagdown}}$$

(1)   (2)

amalgam (0.02 g.-atom Al in 2% aqueous $HgCl_2$).[2] The reaction is stereospecific: Z-1,2-diphenylvinyl phenyl sulfone gives the E-olefin exclusively. $LiAlH_4$–$CuCl_2$ (4:8 mixture)[3] can also be used, but yields are definitely lower (about 60%).

[1]V. Pascali and A. Umani-Ronchi, *J.C.S. Chem. Comm.*, 351 (1973).
[2]E. J. Corey and M. Chaykovsky, *Am. Soc.*, **87**, 1345 (1965).
[3]T. Mukaiyama, K. Narasaka, K. Maekawa, and M. Furusato, *Bull. Chem. Soc. Japan*, **44**, 2285 (1971).

Aluminum azide, $Al(N_3)_3$. Mol. wt. 153.05.

The reagent is prepared[1] *in situ* from $AlCl_3$ and NaN_3 in THF (N_2).

Tetrazole synthesis. Arnold and Thatcher[1] used this reagent to convert acrylonitrile into 5-vinyltetrazole (1).

$$CH_2=CHCN + Al(N_3)_3 \xrightarrow{55\%}$$

(1)
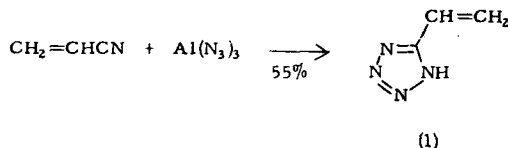
Ammonium azide in DMF has been used also for conversion of nitriles into tetrazoles.[2] This reagent, however, cannot be used in the case of unsaturated

β-cyano esters, since it causes elimination of cyanide ion. In this case aluminum azide is the reagent of choice. However, isomerization precedes formation of the tetrazole. Thus treatment of either ethyl *cis*-3-cyanoacrylate (2) or the *trans*-isomer (3) gives ethyl *trans*-5-tetrazole acrylate (4) in about 30% yield. Rearrangements were observed in the case of other related β-cyano esters.[3]
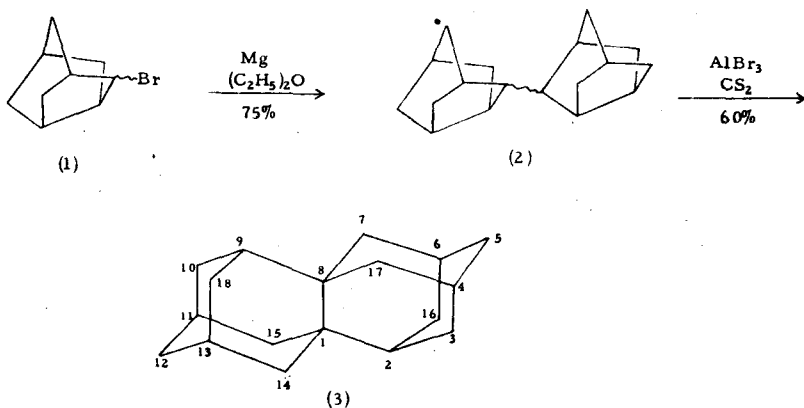

(2)   (4)   (3)
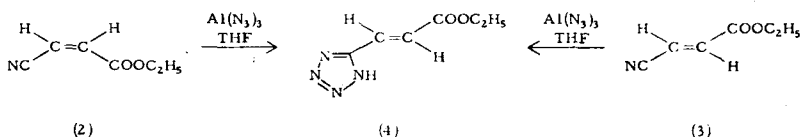
[1]C. Arnold, Jr., and D. N. Thatcher, *J. Org.*, **34**, 1141 (1969).
[2]W. G. Finnegan, R. A. Henry, and R. Lofquist, *Am. Soc.*, **80**, 3908 (1958).
[3]E. R. Wagner, *J. Org.*, **38**, 2976 (1973).

Aluminum bromide, 1, 22–23; **2,** 19–21; **3,** 7; **4,** 10.

[2]*Diadamantane.*[1] This first member (3) of a new class of diadamantoid hydrocarbons has been synthesized as shown.[2]

(1)   (2)

(3)

[1]IUPAC name is hexacyclo[9.3.1.1$^{2.6}$.1$^{4.8}$.1$^{9.13}$.0$^{1.8}$]octadecane.
[2]W. D. Graham, P. v. R. Schleyer, E. W. Hagaman, and E. Wenkert, *Am. Soc.*, **95**, 5785 (1973).

Aluminum chloride, 1, 24–34; **2,** 21–23; **3,** 7–9; **4,** 10–15.

Diels–Alder catalyst (**1,** 31–32; **2,** 21–22; **3,** 8–9; **4,** 10–11). In a recent synthesis of α-damascone (7) by Cookson and Tuddenham,[1] the key step was the Diels–Alder reaction of the dienone (1) with 2-methyl-1-propene catalyzed by AlCl₃. The reaction proceeds in CH₂Cl₂ at 25°. Five products, (2)–(6), were

(1)   + (CH₃)₂C=CH₂   AlCl₃ CH₂Cl₂, 25°   →   (a)   →

(2)   (3)   (4)   (5)

(7)   (6)
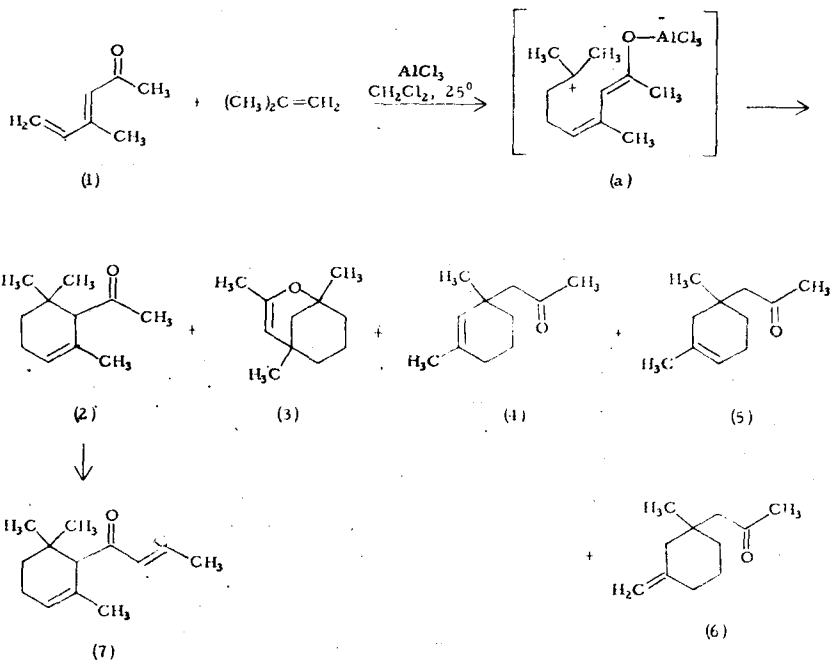
obtained in the ratio 20:55:15:6:4. The formation of the products can be explained on the assumption that the zwitterion (a) is an intermediate.

Adduct (2) was transformed into α-damascone (7) by aldol condensation with acetaldehyde.

Ene catalyst.[2] Aluminum chloride catalyzes the ene reaction of olefins with moderately active enophiles. Thus (−)-β-pinene reacts with methyl acrylate at room temperature in the presence of aluminum chloride to give the adduct (1) in 70% yield.


(1)
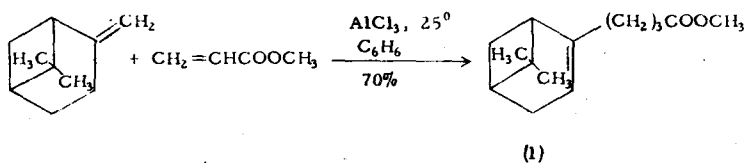
Fries rearrangement[3] *and Friedel–Crafts cyclization.* 7-Hydroxyindane-1-one (3) can be obtained from phenyl β-chloropropionate (1) in one step by use of aluminum chloride if the temperature is controlled carefully: The mixture is

heated at 90–100° for 1 hr.; then the temperature is raised gradually to 160° over a period of 2 hr.; the temperature is controlled at this level for 1 hr., and then the reaction is heated at 180° for 1 hr.[4] If the reaction is carried out in two distinct steps, the overall yield is 20%.[5]
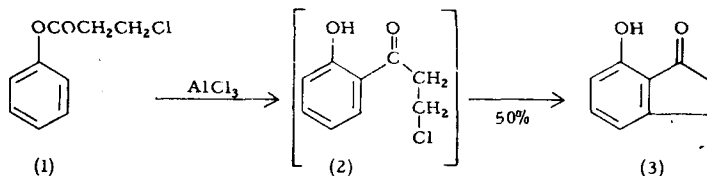
Intramolecular Friedel–Crafts acylation.[6]   Attempted cyclodehydration of (1) to (3, acephenanthrene-5-one) with PPA, HF, $SOCl_2$–$SnCl_4$, PCl_5–$SnCl_4$, or $AlCl_3$ failed to give satisfactory yields. The desired transformation was effected by conversion of (1) to the acid chloride (2), followed by treatment with aluminum chloride in carbon disulfide.
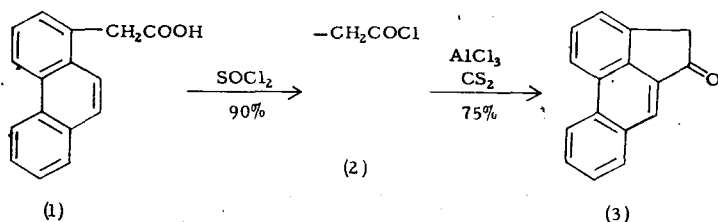
Intramolecular cyclization.[7]   Treatment of the amino enol ether (1) with $AlCl_3$ in CH_2Cl_2 at 4–6° gives the bicyclic amine (2; 5-methoxy-6-methyl-6-azabicyclo[3.2.1]octane) in 20% yield. The main product is the ketone (3).
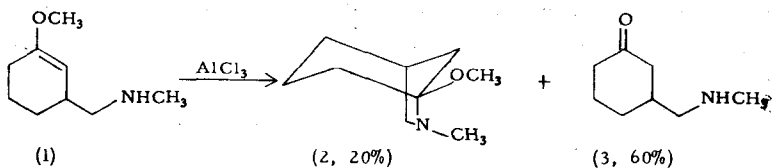
Rearrangement of xanthates.[8]   Xanthates rearrange to dithiolcarbonates when treated with a molar equivalent of aluminum chloride in CS_2.